

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 18-936/S-054**

**CLINICAL PHARMACOLOGY  
BIOPHARMACEUTICS REVIEW**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**NDA 18-936/SCM-054****Prozac® (Fluoxetine HCl)****(40 & 60mg Capsules)****Type of submission: Supplement S-054****Submission Date: 2/17/1999, 4/5/1999****Sponsor: Lily Research Lab.****INDICATION: antidepressant/ICD/Bulimia agent****REVIEWER: Rae Yuan, Ph.D.****Draft Review: 3/19/99, 4/12/99**

The sponsor had requested for biowaiver on 40 and 60mg capsule formulations in the submission dated 6/17/1998. The request was not approved based on the failed dissolution profile comparison, nonlinear kinetics and compositional disproportionality between the proposed products and the approved products (see the review dated 11/23/1998). On 2/5/1999, a meeting was held between the sponsor and the agency to discuss the acceptability of the new dosage strengths (see the meeting minutes). During the meeting, it was agreed that the information on the new strengths in vivo is needed for its approval, a request to which this submission responds. In this submission, the sponsor re-analyzed the data from study 38 (submitted in the original NDA), to provide in vivo evidence on bioequivalency of the 60mg and 20mg fluoxetine capsule dosage forms.

Study 38 was a bioavailability and dose proportionality study with parallel design in 28 healthy subjects in 7 cohorts. Each cohort consists of 4 subjects receiving single dose of fluoxetine concurrently with deuterium labeled fluoxetine. The treatments in the 60mg treatment group and 20mg group are as follows:

Treatment Arm	Number of Subjects	Unlabeled Fluoxetine Capsule	Labeled Fluoxetine Solution
60mg Capsule	4	60 mg	30 mg
20mg Capsule	4	20mg	20 mg

The sponsor compared the PK parameters in these two groups and conducted a statistical analysis on the C<sub>max</sub> and AUC<sub>inf</sub> ratios of the unlabeled to labeled drug, and the results are as follows:

Parameters	Point Estimate	90% Confidence Interval
Ratio of C <sub>max</sub> fluoxetine	1.05	0.94-1.16
Ratio of AUC fluoxetine	1.10	0.97-1.23
Ratio of C <sub>max</sub> norfluoxetine	0.97	0.84-1.10
Ratio of AUC norfluoxetine	1.05	0.87-1.23

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Since it appears that in the submission dated 2/17/99, the sponsor used the untransformed data for 90% confidence interval analysis, we consulted the QMSR group on further data analysis using log-transformed data. Dr. Chuanpu Hu provided the following results, using the ratio of the unlabeled to the labeled:

Fluoxetine				
Dose	AUC ratio	90% C.I.	Cmax ratio	90% C.I.
60 mg:30 mg	0.93	0.83-1.05	0.98	0.86-1.11

Norfluoxetine				
Dose	AUC ratio	90% C.I.	Cmax ratio	90% C.I.
60 mg:30 mg	1.19	0.86-1.64	0.94	0.84-1.06

In study 38, the subjects were given fluoxetine at a total dose of 40 and 90 mg, the dose range at which the sponsor showed that AUC was nonlinear to dose (see the attachment). According to the literature (J. Clin. Pharmacol. 26:419-24, 1986), loss of the linearity invalidates the isotope method in BE study, or at the very best, requires appropriate corrections on the pharmacokinetic data. The reviewer consulted with Dr. John Strong of the Office of Testing and Research, who has extensive experience in stable isotope studies, on using such approach in fluoxetine BE evaluation. According to Dr. Strong, since the AUC ratio of the unlabeled to the labeled products is linear to the dose ratio for both the parent drug and norfluoxetine metabolite (see the attachment), this validates the use of isotope approach for assessing BE for fluoxetine. Dr. Strong also presented a simulation study during an internal meeting on 3/25/99, attended by Drs. Lesko, Mehta, Sahajwalla, Yuan. Dr. Strong showed that for a drug that follows Michaelis Menton kinetics, the AUC ratio is a sensitive parameter to Vmax (an indicator of total enzyme). That is, AUC ratio is 1 if the enzyme is not saturated and deviates from 1 if the enzyme has 20% saturation. Since the slope of AUC ratio vs. Dose for fluoxetine is close to 1, the kinetic of fluoxetine is linear at the studied dose range. The observed nonlinearity, thus, may be due to the inter-individual variations on metabolizing enzyme CYP2D6 among the subjects.

The stable isotope approach has been accepted in the office of Clinical Pharmacology and Biopharmaceutics to assess BE for a new drug product. In this submission, the sponsor also provided results on all the conventional BE studies conducted to compare different fluoxetine formulations. They demonstrated that being a highly soluble and highly permeable drug, fluoxetine has been shown to be bioequivalent in a conventional approach regardless of formulations.

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**Comments:**

1. Although study 38 had only 4 subjects per group enrolled in the study, it demonstrated that this was adequate to meet the bioequivalence criteria.
2. Dr. Hu's report indicates that the comparison on norfluoxetine fails to meet BE criteria. The sponsor reasoned that the assay on norfluoxetine may not be reliable due to the lack of analytical standard for this metabolite. Besides, the metabolite pharmacokinetics are very subjective to an individual's physiological/biological feature. As a result, a larger variation is usually seen in the metabolite PK than the parent compound PK. That is, passing BE criteria for the parent compound may not guarantee the passing for the metabolite. As for fluoxetine, since the analytical assay for the parent compound is sensitive and specific, the product performance can be assessed mainly on the rate and extent of absorption of the parent drug.

**Recommendation:**

The proposed 60mg product is deemed bioequivalent to the approved 20mg product.

Rae Yuan, Ph.D. 151

Team Leader: Chandra Sahajwalla, Ph.D. 15

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Mehta); CDR (Barbara Murphy)

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NDA ORIG 18-936/S-054

IND: DIV FILE

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HFD-120/PDavid

HFD-860/LLesko/MMehta/CSahajwalla/RYuan/

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MEETING MINUTES

NOV 23 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

**NDA 18-936/SCM-054**

**Prozac® (Fluoxetine HCl)**

(40 & 60mg Capsules)

Type of submission: Supplement (new dosage strengths)

Submission Date: June 17, 1998; Nov. 13, 1998

Sponsor: Lily Research Lab.

INDICATION: antidepressant/ICD/Bulimia agent

REVIEWER: Rae Yuan, Ph.D.

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The currently approved marketed dosage forms of fluoxetine include 10 & 20 mg capsules (Pulvules®) and an oral liquid formulation. To reduce the number of capsules needed to be administered at high dose, the sponsor seeks an approval for two new strengths (40 and 60 mg) without bio-studies. The reasons given by the sponsor for such a waiver are:

- *The high aqueous solubility and highly permeable nature of the drug, and rapid dissolution of the products* (BCS Class I definition);
- *Dose linearity demonstrated for 20-80 mg capsules* (study submitted in the original NDA 18-936, see Attachment for the results);
- *Comparable qualitative composition of the formulations.* (The proposed 60-mg capsule has the identical formulation as the one used in the dose proportionality study, with the exception of capsule shell color. The proposed capsule has the same color as the approved 20 mg capsule. The proposed 40-mg capsule has excipients amount slightly different from the one listed in the dose proportional study. But these differences fall within SUPAC Level 1 category; see Attachment for composition); However, it should be noted that 40 and 60 mg capsule formulations being proposed are not compositionally proportional to the approved 10 and 20 mg capsule formulations.
- *Comparable dissolution for the 10-, 20-, 40- and 60 mg capsules, based on one point comparison at 30 min.* (see Attachment for dissolution results).
- *Previously demonstrated similar and favorable bioavailability of 20-, 40-, and 60-mg capsules.* (see Attachment for the results).

Since the dissolution data submitted was based on only 6 units and dissolution profile comparisons were not carried out by the sponsor, this reviewer contacted the sponsor and requested that the sponsor provide a complete information before a waiver request can be considered. The sponsor requested a telecon with the OCPB review team, which occurred at 9:30 am, Oct. 23, 1998. The sponsor was reluctant to carry out f2 comparison, as they indicated during the telecon that the dissolution profiles might not be comparable between the proposed products and the approved products. The sponsor consented on the dissolution comparison, but requested it be performed at 0.1 N HCl, as they reasoned that this drug is BCS class I compound. But we informed them that dissolution profile comparison had to be carried out in three different pH media.

On Nov. 13, 1998, the sponsor submitted the f2 comparison of the dissolution profile generated by using proposed dissolution condition. The f2 comparison shows that dissolution profiles of 40 mg capsule is different from 10 (f2=~~34~~), 20 mg (f2=39), and 60 mg (f2=44), although 60 mg is similar to 10 mg (f2=52) and 20 mg (f2=70). It is noted that the dissolution comparison was conducted in only one dissolution medium. The sponsor argued that the dissolution rate is not a critical determinant of the rate or extent of absorption of fluoxetine, and the difference in dissolution at earlier time point is expected for a larger strength dosage form. As the proposed capsules exhibit the same dissolution specification as the existing 10 and 20 mg capsules, the sponsor argued for a waiver of in vivo bioequivalence testing on the proposed products.

**Comments:**

Traditionally, when a higher strength has been approved, a bio-waiver for lower strengths can be granted, provided that formulation is compositionally proportionally to the approved products and dissolution profiles obtained by performing dissolution on 12 units have been shown to be comparable (CFR 320.22 (d) (2)). The sponsor is requesting a waiver of bioequivalence study for capsule strengths higher than what has been approved.

The proposed formulations are not compositionally proportional, and the dissolution data provided by the sponsor indicate that the dissolution profiles are not comparable. Further, this waiver request does not fall under SUPAC-IR guidance, since this is not post-approval changes but a request for approval for higher strength.

**Recommendation:**

The biowaiver for the proposed higher strengths of Prozac capsule at 40 and 60 mg is NOT recommended, because the proposed formulations are not compositionally proportional to the approved formulation. The sponsor is requested to conduct a bioequivalency study using the highest proposed strengths (60 mg). The sponsor may request a waiver for the lower strengths (40 mg) and provide the following information along with the waiver request:

- (1) Compositional proportionality between 40 and 60 mg capsules;
- (2) Comparable dissolution profiles based on 12 units in 3 different pH media (0.1N HCl, water and phosphate buffer). F2 values should be calculated for each medium to demonstrate the comparability of dissolution profiles between the 40 mg and 60 mg capsules.

Rae Yuan, Ph.D.

Team Leader: Chandra Sahajwalla, Ph.D.

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